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Published in:
Pulmonary Pharmacology & Therapeutics

DOI:
[10.1016/j.pupt.2015.02.008](https://doi.org/10.1016/j.pupt.2015.02.008)

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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2015

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Kerstjens, H. A. M., Deslee, G., Dahl, R., Donohue, J. F., Young, D., Lawrence, D., & Kornmann, O. (2015). The impact of treatment with indacaterol in patients with COPD: A post-hoc analysis according to GOLD 2011 categories A to D. *Pulmonary Pharmacology & Therapeutics*, 32, 101-108.
<https://doi.org/10.1016/j.pupt.2015.02.008>

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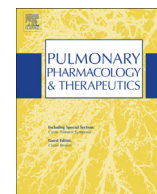
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The impact of treatment with indacaterol in patients with COPD: A post-hoc analysis according to GOLD 2011 categories A to D



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ARTICLE INFO

Article history:

Received 4 November 2014

Received in revised form

18 February 2015

Accepted 22 February 2015

Available online 3 March 2015

Keywords:

Chronic obstructive pulmonary disease

GOLD categories

Indacaterol

Lung function

Symptoms

ABSTRACT

Background: Indacaterol is an inhaled, once-daily, ultra-long-acting β_2 -agonist for the treatment of chronic obstructive pulmonary disease (COPD). We report on the effectiveness of indacaterol and other bronchodilators compared with placebo in patients across the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2011 categories A to D.

Methods: A post-hoc, subgroup pooled analysis of 6-month efficacy data from three randomized, placebo-controlled, parallel-group studies involving 3862 patients was performed across GOLD 2011 categories A to D, according to baseline forced expiratory volume in 1 s (FEV₁) % predicted, modified Medical Research Council (mMRC) dyspnea scale, and exacerbation history in the 12 months prior to entry. Efficacy of once-daily indacaterol 150 and 300 μ g, open-label tiotropium 18 μ g, twice-daily salmeterol 50 μ g, and formoterol 12 μ g was compared with placebo. End points analysed were trough FEV₁, transition dyspnea index (TDI), and St George's Respiratory Questionnaire (SGRQ) total score, all at Week 26, and mean rescue medication use over 26 weeks.

Results: Indacaterol 150 and 300 μ g significantly improved FEV₁, compared with placebo across all GOLD groups. Indacaterol 150 and 300 μ g also significantly improved TDI, SGRQ total score, and mean rescue medication use compared with placebo across most GOLD subgroups.

Conclusions: Treatment selection according to patient's symptoms as well as lung function is an important consideration in maintenance treatment of COPD. Indacaterol 150 and 300 μ g effectively improved lung function and symptoms in patients across all GOLD 2011 categories.

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1. Introduction

A major revision to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy document was published in 2011, in

which patients with chronic obstructive pulmonary disease (COPD) were classified according to symptoms and exacerbation risk, rather than lung function alone [1]. This document included suggestions for treatment choices, however, these recommendations were based on studies with populations selected with previous GOLD classifications, according to FEV₁ % predicted alone, and had no direct backing with data [2–4]. The authors of the GOLD strategy document anticipated that the new classification scheme would encourage new studies to generate more supporting evidence. Ultimately, these should be prospective randomized controlled trials selecting patients based on the new classification; however, there will be a long lead time before publication of data from such studies. In the meantime, existing data sets can be re-analyzed

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post-hoc to see whether the classification A to D is indeed useful in categorizing patient groups with different impact of COPD and in guiding therapeutic choices. Assessing the effects of treatments per category A to D should help in building the evidence base under the choices made in the GOLD document.

Therefore, the purpose of this post-hoc analysis was to assess the efficacy of the once-daily long-acting β_2 -agonist (LABA) indacaterol versus placebo across different patient categories as closely aligned to GOLD 2011 as the data allowed. The magnitude of effect was also compared with the currently available bronchodilators, twice-daily LABAs formoterol and salmeterol, and the once-daily long-acting muscarinic antagonist (LAMA) tiotropium.

Data from three clinical studies [5–7] were pooled for this post-hoc analysis. Endpoints included measurement of airflow limitation using trough FEV₁ (mean of 23 h 10 min and 23 h 45 min post-dose readings), breathlessness symptoms using the transition dyspnea index (TDI), and health status using St Georges Respiratory Questionnaire (SGRQ) total score, all at week 26, and the mean rescue medication use (salbutamol/albuterol) over 26 weeks.

2. Methods

2.1. Study design

We conducted a pooled analysis of 6-month patient-level efficacy data from three Phase III, randomized studies, for which primary outcomes have been previously published. The studies selected had similar inclusion and exclusion criteria, similar end-points, and included the main bronchodilators used in the treatment of COPD. These studies were: INdacaterol: Value in COPD: Longer term Validation of Efficacy and safety (INVOLVE, Clinicaltrials.gov registration number NCT00393458), a double-blind comparison of indacaterol 300 μ g or 600 μ g once daily with placebo and formoterol 12 μ g twice daily for 52 weeks (data from the indacaterol 600 μ g treatment group are excluded from this pooled analysis as this dose is not approved in any country) [5]; INdacaterol versus tiotropium to Help Achieve New COPD treatment Excellence (INHANCE, NCT00463567), which compared double-blind indacaterol 150 μ g or 300 μ g once daily with placebo and open-label tiotropium 18 μ g once daily for 26 weeks [6]; and INdacaterol: efficacy evaluation usInG 150 μ g doses with COPD PatientS (INLIGHT 2, NCT00567996), a 26-week study comparing double-blind indacaterol 150 μ g once daily with placebo and salmeterol 50 μ g twice daily [7].

2.2. Patients

All three studies sought to enroll patients with a clinical diagnosis of moderate-to-severe COPD [using the GOLD 2005 criteria, i.e., post-bronchodilator FEV₁ <80% and \geq 30% of the predicted normal value, post-bronchodilator FEV₁/forced vital capacity (FVC) < 70%]. Other inclusion criteria were: males and females aged \geq 40 years with a smoking history of at least 20 pack-years. All had trough FEV₁ as primary end-point. Study designs and detailed inclusion and exclusion criteria of the individual studies have been published previously [5–7].

For the purposes of this analysis, patients were classified as A, B, C, or D using GOLD 1–4 classification of airflow limitation, history of exacerbations, and patient reported symptoms, according to the following criteria: category A: mMRC < 2, and GOLD 1 or 2 (FEV₁ \geq 50% predicted), and no history of exacerbations in the previous year; category B: mMRC \geq 2, and GOLD 1 or 2, and no history of exacerbations in the previous year; category C: mMRC < 2, and GOLD 3 or 4 (FEV₁ < 50% predicted) and/or one or more exacerbations in the previous year; and category D:

mMRC \geq 2, and GOLD 3 or 4 and/or one or more exacerbations in the previous year. The assessment pointing to the highest risk was used, thus matching the GOLD recommendations.

An adjustment had to be made as exacerbation history (in the 12 months before recruitment) was only available as “Yes” or “No” in the study database, whereas the GOLD strategy document classifies patients according to the number of exacerbations (0–1 or 2+).

Inhaler technique in all three studies was assessed by investigators/staff at the screening and randomization visits. Study drug compliance was assessed by the investigator and/or center personnel at designated visits by recording capsule counts/dose counter readings, as well as information provided by the patient/caregiver.

All participants in the three studies provided written informed consent, and all study protocols were approved by the independent ethics committee/institutional review board at each study site in the respective participating country. All three studies were conducted in compliance with good clinical practice and in accordance with the Declaration of Helsinki.

2.3. End points

2.3.1. Lung function

The primary end point analysed was trough FEV₁ at Week 26 measured using standard spirometry according to ATS/ERS guidelines (mean of 23 h 10 min and 23 h 45 min post-dose readings, based on the time of the previous morning dose. This time point was 12 h after the second dosing for the twice daily bronchodilators formoterol and salmeterol). A difference versus placebo in trough FEV₁ of 120 mL was considered as the minimum clinically important difference (MCID). This is the mid-point of the 100–140 mL range reported as the MCID by the American Thoracic Society/European Respiratory Society [8].

2.3.2. Health status and dyspnea

Health status was assessed using the SGRQ questionnaire and dyspnea was assessed using the TDI questionnaire. SGRQ total score and the odds ratio (OR) for the percentage of patients achieving \geq 4 unit improvement from baseline (the MCID for SGRQ [9]) and TDI total score and OR for the percentage of patients achieving the MCID of \geq 1 unit improvement from the Baseline Dyspnea Index (BDI) score [10] were assessed at Week 26.

2.3.3. Rescue medication

Patients recorded their use of rescue medication (number of puffs) twice daily in patient diaries. Rescue medication (salbutamol/albuterol MDI) use in terms of change from baseline in number of puffs/day and % days with no rescue medication use was measured over 26 weeks.

2.3.4. Statistical analysis

Trough FEV₁ after 26 weeks of treatment was analyzed using a mixed-model analysis of covariance (ANCOVA), with treatment, baseline ICS use, smoking status, and study as fixed effects and baseline FEV₁ and FEV₁ reversibility as covariates. Center nested within country was included as a random effect. To assess the treatment effect across the GOLD risk categories, a fixed effect for risk group and a treatment by risk group interaction were included in the model. The same model (with appropriate baseline) was used to analyze SGRQ and TDI total scores as well as change from baseline in puffs of rescue medication per day and percentage of days with no rescue use. Data are presented as least squares means with standard errors (SE) or associated 95% confidence intervals (CI) for differences between treatments. The proportion of patients achieving MCID in FEV₁, TDI, and SGRQ was analyzed using a

Table 1

Patient characteristics at baseline by GOLD 2011 category in the pooled analysis data set.

| GOLD 2011 category | A | B | C | D |
|--|--------------|--------------|--------------|--------------|
| N | 1134 | 1008 | 622 | 1078 |
| Age, mean (SD) years | 63 (8.9) | 64 (9.2) | 62 (8.4) | 64 (8.3) |
| ≥65, % | 46.5 | 51.9 | 42.9 | 47.2 |
| Sex, % male | 70.2 | 63.5 | 78.0 | 75.1 |
| Current smoker, % | 44.7 | 42.3 | 44.7 | 43.8 |
| Mean (SD) pack years | 46 (28.0) | 46 (23.7) | 44 (21.8) | 46 (21.8) |
| Inhaled corticosteroid use, yes (%) | 39.4 | 39.3 | 52.3 | 50.1 |
| Spirometry – post salbutamol administration | | | | |
| FEV ₁ ≥ 50% predicted, % | 100.0 | 100.0 | 6.3 | 5.6 |
| FEV ₁ <50% predicted, % | 0.0 | 0.0 | 93.7 | 94.4 |
| mMRC score | | | | |
| <2 | 1134 | 0 | 622 | 0 |
| ≥2 | 0 | 1008 | 0 | 1078 |
| Patients with exacerbation in past year, n (%) | 0 | 0 | 72 (11.6) | 149 (13.8) |
| Mean (SD) duration of COPD, years | 6.0 (6.07) | 6.8 (6.45) | 7.0 (6.98) | 7.4 (6.20) |
| Mean (SD) FEV ₁ predicted, % | 65.2 (9.57) | 63.2 (9.71) | 43.2 (8.15) | 41.2 (7.92) |
| Mean (SD) FEV ₁ /FVC ratio, % | 57.3 (8.39) | 56.8 (8.78) | 47.5 (8.84) | 46.1 (9.63) |
| Baseline rescue use, mean puffs/day | 2.2 (2.67) | 3.3 (3.42) | 3.1 (3.27) | 4.6 (4.08) |
| Mean (SD) baseline SGRQ total score | 34.3 (15.68) | 48.7 (16.80) | 38.8 (15.49) | 54.0 (16.31) |
| Mean (SD) BDI total score | 8.0 (1.92) | 5.9 (1.88) | 7.2 (1.90) | 5.3 (1.88) |

BDI, baseline dyspnea index; FEV₁, forced expiratory volume in 1 s; SD, standard deviation; SGRQ, St George's Respiratory Questionnaire.

logistic regression model with the results presented as ORs with associated 95% CI for the analysis of percentages of patients. All covariates were the same as the ANCOVA model with the exception of country which, due to convergence issues, was replaced by region (North America, South America, Europe, other).

All analyses were performed using SAS version 9.3. No powering or sample size calculations were performed for these post-hoc analyses, and no adjustment was made for multiplicity.

3. Results

3.1. Patients

Patient distribution across the four GOLD 2011 categories is shown in Table 1. Mean age and current smoking status were similar across the categories. Patient numbers by treatment used in the analysis are shown in Table 2. Inhaler technique in all patients was regarded as acceptable according to recommended use. Compliance to treatment was high across all three studies, over 96% for all treatment groups.

3.2. Trough FEV₁

The highest overall improvement in trough FEV₁ versus placebo at Week 26 for all bronchodilators except formoterol was seen in Group A (Fig. 1). In all categories, indacaterol 150 µg improved trough FEV₁ versus placebo by a statistically significant ($p < 0.0001$) and clinically relevant (>120 mL) amount. Improvements with other treatments were not as consistent across categories; not

achieving clinical significance in all categories or significance against placebo. The ORs for achieving MCID versus placebo were similar with indacaterol 150 µg, 300 µg, and tiotropium (Fig. 2).

3.3. SGRQ

Indacaterol 150 µg was the only bronchodilator to exhibit a significant improvement in SGRQ versus placebo in all four GOLD categories. All active treatments gave statistically significant improvements versus placebo in categories B and C (Fig. 3). The ORs for percentage of patients achieving the MCID are presented in Fig. 4.

3.4. TDI

Indacaterol 300 µg achieved a significant mean treatment effect versus placebo in excess of the MCID consistently across all categories (Fig. 5). Indacaterol 150 µg achieved a significant mean treatment effect versus placebo in excess of the MCID in categories A, B, and C. Patients receiving indacaterol 150 and 300 µg were significantly more likely to experience a clinically relevant improvement in TDI than those receiving placebo in all GOLD categories (Fig. 6).

3.5. Rescue salbutamol use

In all GOLD categories, the mean rescue medication use was statistically significantly reduced with indacaterol 150 and 300 µg, formoterol, and salmeterol versus placebo ($p < 0.0001$, Fig. 7). The %

Table 2

Patient numbers by treatment in GOLD 2011 category.

| Treatment | A | B | C | D | Total sample |
|--------------------|--------------------------------------|--------------------------------------|-------------------------------------|--------------------------------------|----------------------------|
| | n (% of treatment group) N = 1134 | n (% of treatment group) N = 1008 | n (% of treatment group) N = 622 | n (% of treatment group) N = 1078 | n (% of total) N = 3862 |
| Indacaterol 150 µg | 223 (29.9) | 203 (27.2) | 118 (15.8) | 201 (26.9) | 746 (19.3) |
| Indacaterol 300 µg | 234 (28.6) | 232 (28.3) | 133 (16.2) | 217 (26.5) | 819 (21.2) |
| Formoterol 12 µg | 106 (26.6) | 115 (28.9) | 63 (15.8) | 114 (28.6) | 398 (10.3) |
| Salmeterol 50 µg | 110 (33.1) | 65 (19.6) | 61 (18.4) | 96 (28.9) | 333 (8.6) |
| Tiotropium 18 µg | 111 (27.0) | 121 (29.4) | 62 (15.1) | 117 (28.5) | 415 (10.8) |
| Placebo | 350 (30.7) | 272 (23.9) | 185 (16.2) | 333 (29.2) | 1151 (29.8) |

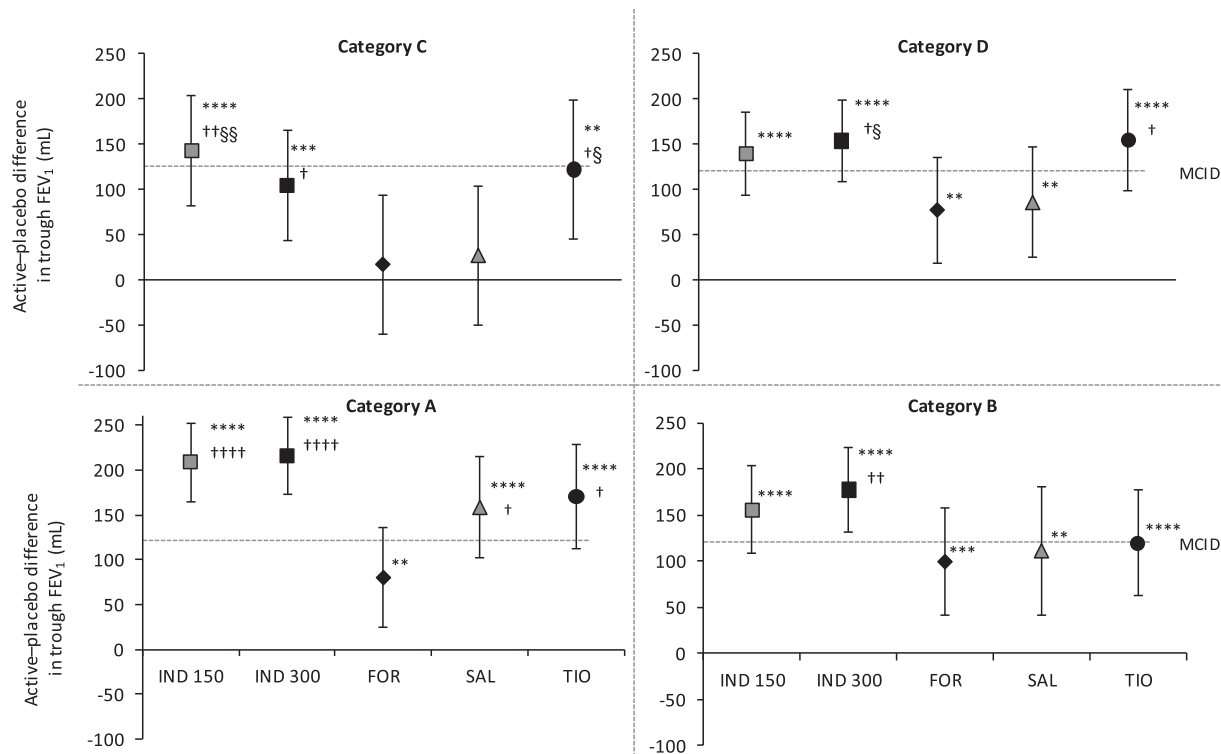


Fig. 1. Effect of treatments (active–placebo difference) on trough FEV₁ at Week 26 by GOLD 2011 category. Data are least squares means \pm 95% confidence interval. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$ versus placebo; † $p < 0.05$, †† $p < 0.01$, ††† $p < 0.0001$ for difference versus formoterol; ‡ $p < 0.05$ for difference versus tiotropium; § $p < 0.05$, §§ $p < 0.01$ for difference versus salmeterol. Dashed line represents the minimum clinically important difference (MCID) between active and placebo treatments. FEV₁, forced expiratory volume in 1 s; FOR, formoterol 12 μ g; IND 150, indacaterol 150 μ g; IND 300, indacaterol 300 μ g; SAL, salmeterol 50 μ g; TIO, tiotropium 18 μ g.

days without rescue medication use was significantly greater than placebo for both indacaterol doses and for formoterol, but not consistently so for salmeterol and tiotropium (Supplementary Fig. 1).

4. Discussion

This post-hoc analysis of three pooled clinical studies aimed to compare the LABAs indacaterol, LABAs salmeterol and formoterol, and LAMA tiotropium against placebo in terms of lung function, symptom scores, health-related quality of life, and rescue medication use. All of these measures are important goals in the management of COPD. The current GOLD strategy for COPD treatment emphasizes the need to assess the impact of the disease by patient-reported symptoms through mMRC, CAT or CCQ questionnaires, and the risk of exacerbations in terms of exacerbation history or lung function. These assessments group patients into four categories of COPD severity (A, B, C, and D). On the basis of this categorization, the pooled analysis here allows for the assessment of the effectiveness of indacaterol and other bronchodilators in patients with differing severities of COPD.

Patient distribution in this pooled analysis of three studies illustrates the characteristics of patients with COPD recruited into clinical trials (Table 1). The order of mMRC score from worst to best was D-B-C-A. A similar order was observed for SGRQ and BDI score, partially validating the chosen categorization on the symptom score axis. Mean duration of COPD increased linearly from category A to D, however, there was no large difference between categories. This is consistent with the results from other analyses, suggesting that disease progression is dependent on many factors that are patient specific [11–13]. There was also no clear pattern between the GOLD groups in our analysis in terms of age or smoking status.

ICS use was greater in categories C and D, in line with GOLD recommendations in patients with frequent exacerbation history [1], although a significant percentage of patients were on ICS in categories A and B.

Indacaterol 150 μ g performed well across all categories and consistently achieved improvements in more end points than formoterol, salmeterol, and tiotropium. Overall, in category B (for which a LABA is one of the recommended first choices) indacaterol 150 and 300 μ g consistently gave the greatest improvements compared with placebo in FEV₁, TDI, and rescue medication use. Supporting these data, a network meta-analysis of several trials [14] concluded that indacaterol 150 and 300 μ g were associated with greater improvements in FEV₁ and SGRQ compared with glycopyrronium, tiotropium, salmeterol, and formoterol in patients with moderate-to-severe COPD. The results of the current pooled analysis provide further evidence for the effectiveness of treatment with indacaterol 150 and 300 μ g, in terms of both lung function and symptom scores, across all GOLD subcategories.

Patients in category A, for whom SABA or SAMA is the recommended first choice according to the GOLD strategy, responded remarkably well to all of the active treatments, with significant improvements in lung function, symptoms, and rescue medication use, suggesting a benefit in providing long-acting bronchodilators to these patients. This provides additional support for the statement in the GOLD strategy document that long-acting bronchodilators are more effective than short-acting formulations at producing maintained symptom relief [1]. Patients in categories C and D, for whom the GOLD strategy lists mono-LAMA as one of the treatment options, were also able to gain substantial benefit from LABA monotherapy, although the SGRQ and TDI total scores in category D suggest that intensification of therapy (e.g., LABA and LAMA combination) may be needed.

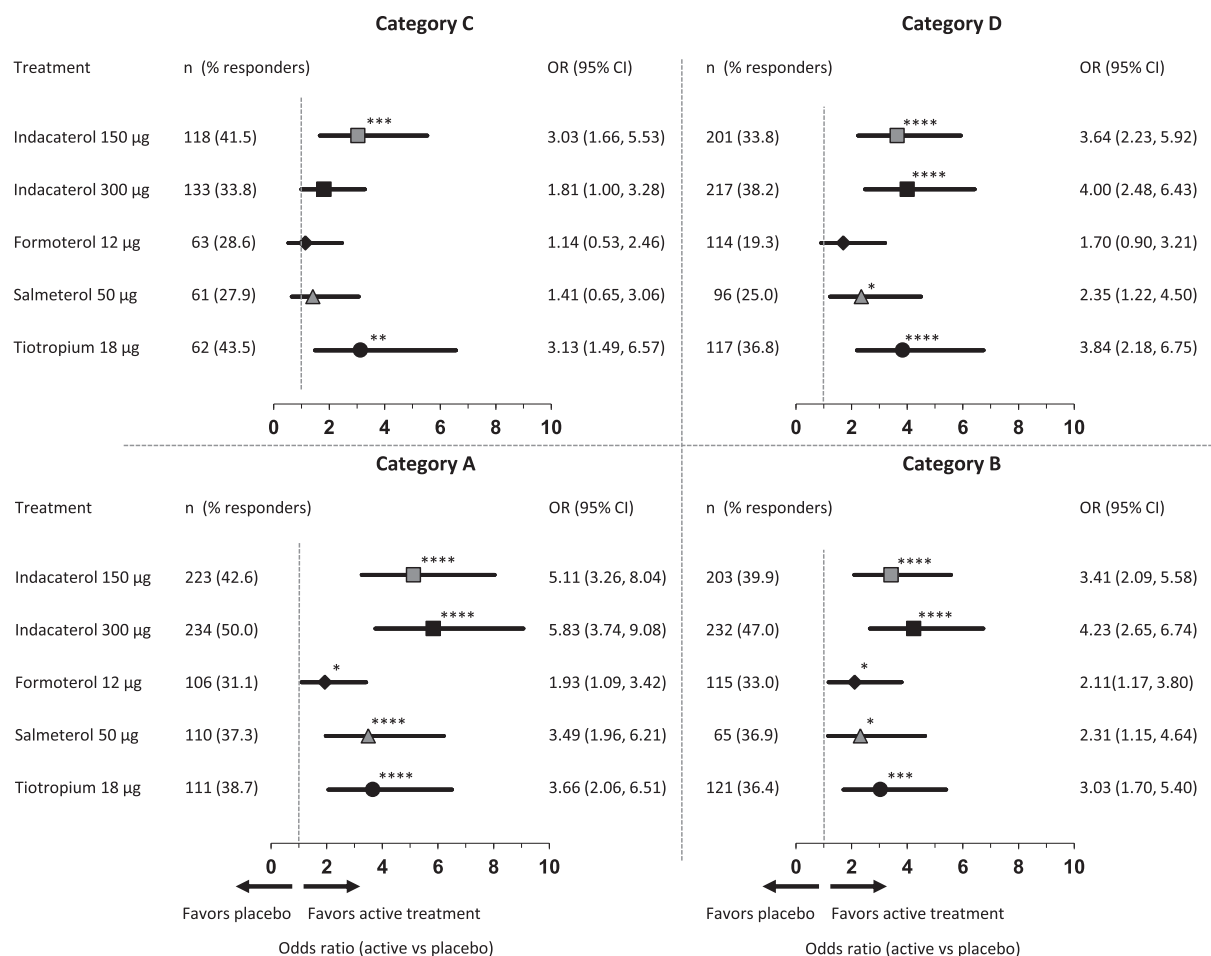


Fig. 2. Odds ratios (active vs placebo) and associated 95% CI for achieving MCID in trough FEV_1 at Week 26 by GOLD 2011 category. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$ versus placebo; FEV_1 , forced expiratory volume in 1 s; MCID, minimum clinically important difference.

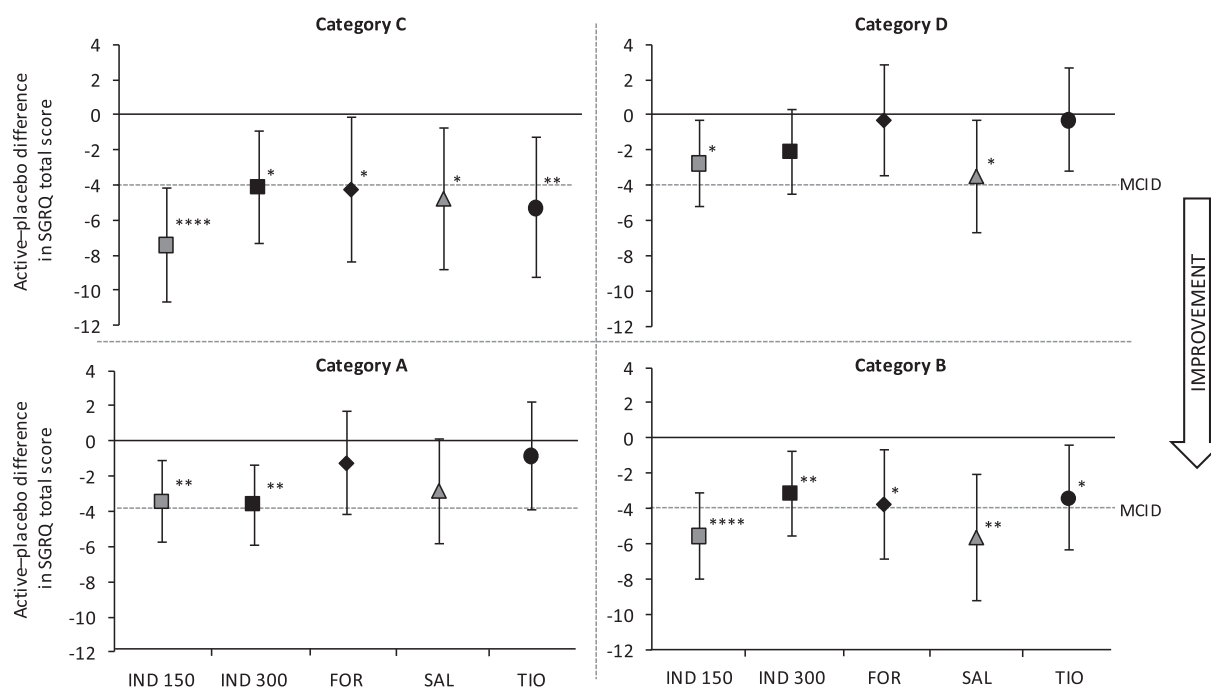


Fig. 3. Effect of treatments (active–placebo differences) on SGRQ total score at 26 weeks by GOLD 2011 category. Data are least squares means \pm 95% confidence interval. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$ versus placebo. Dashed line represents the MCID between active and placebo treatments. FOR, formoterol 12 µg; IND 150, indacaterol 150 µg; IND 300, indacaterol 300 µg; MCID, minimum clinically important difference; SAL, salmeterol 50 µg; SGRQ, St George's Respiratory Questionnaire; TIO, tiotropium 18 µg.

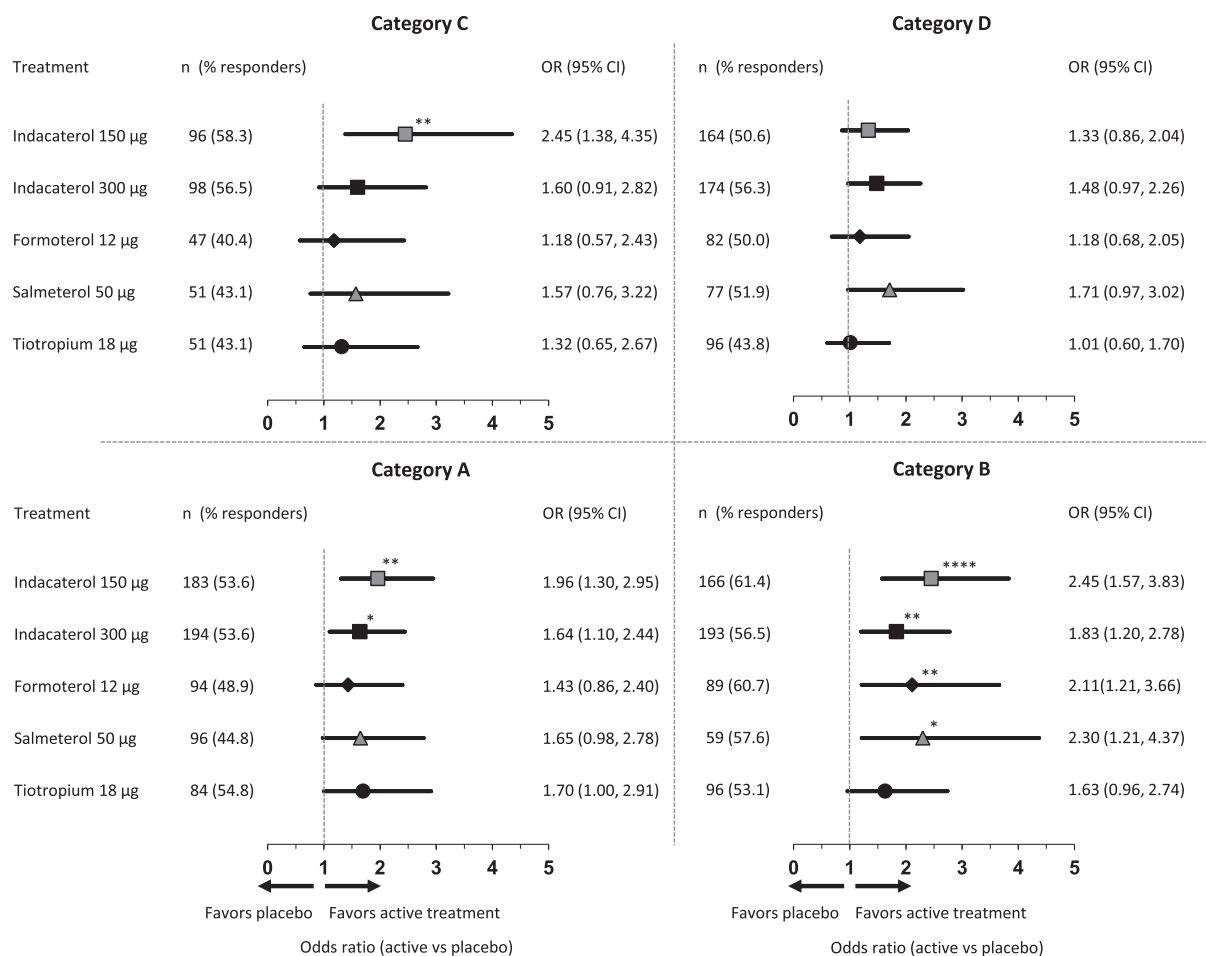


Fig. 4. Odds ratios (active vs placebo) and associated 95% CI for achieving MCID in SGRQ total score (-4 points) at Week 26 by GOLD 2011 category. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.0001$ versus placebo; MCID, minimal clinically important difference; SGRQ, St George's Respiratory Questionnaire.

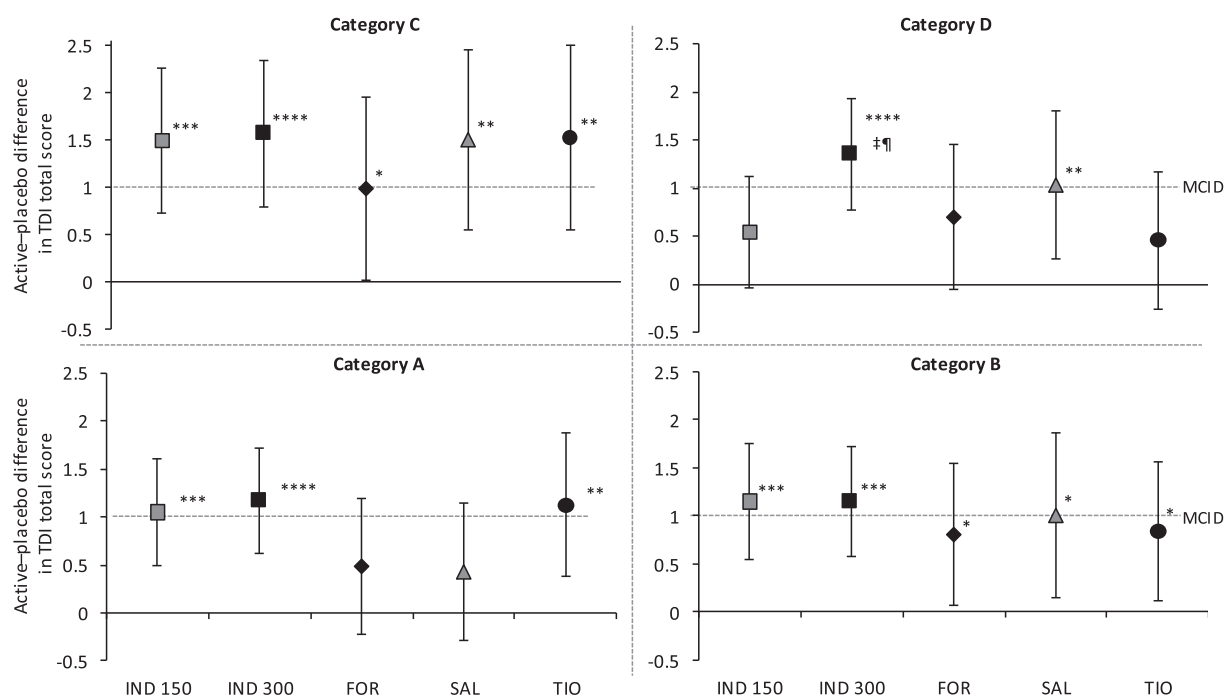


Fig. 5. Effect of treatments (active-placebo differences) on TDI total score at Week 26 by GOLD 2011 category. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$ versus placebo; $^{\dagger}p < 0.05$ for difference versus tiotropium; * $p < 0.05$ versus indacaterol 150 µg. Dashed line represents the MCID between active and placebo treatments. FOR, formoterol 12 µg; IND 150, indacaterol 150 µg; IND 300, indacaterol 300 µg; MCID, minimal clinically important difference; SAL, salmeterol 50 µg; TDI, transition dyspnea index; TIO, tiotropium 18 µg.

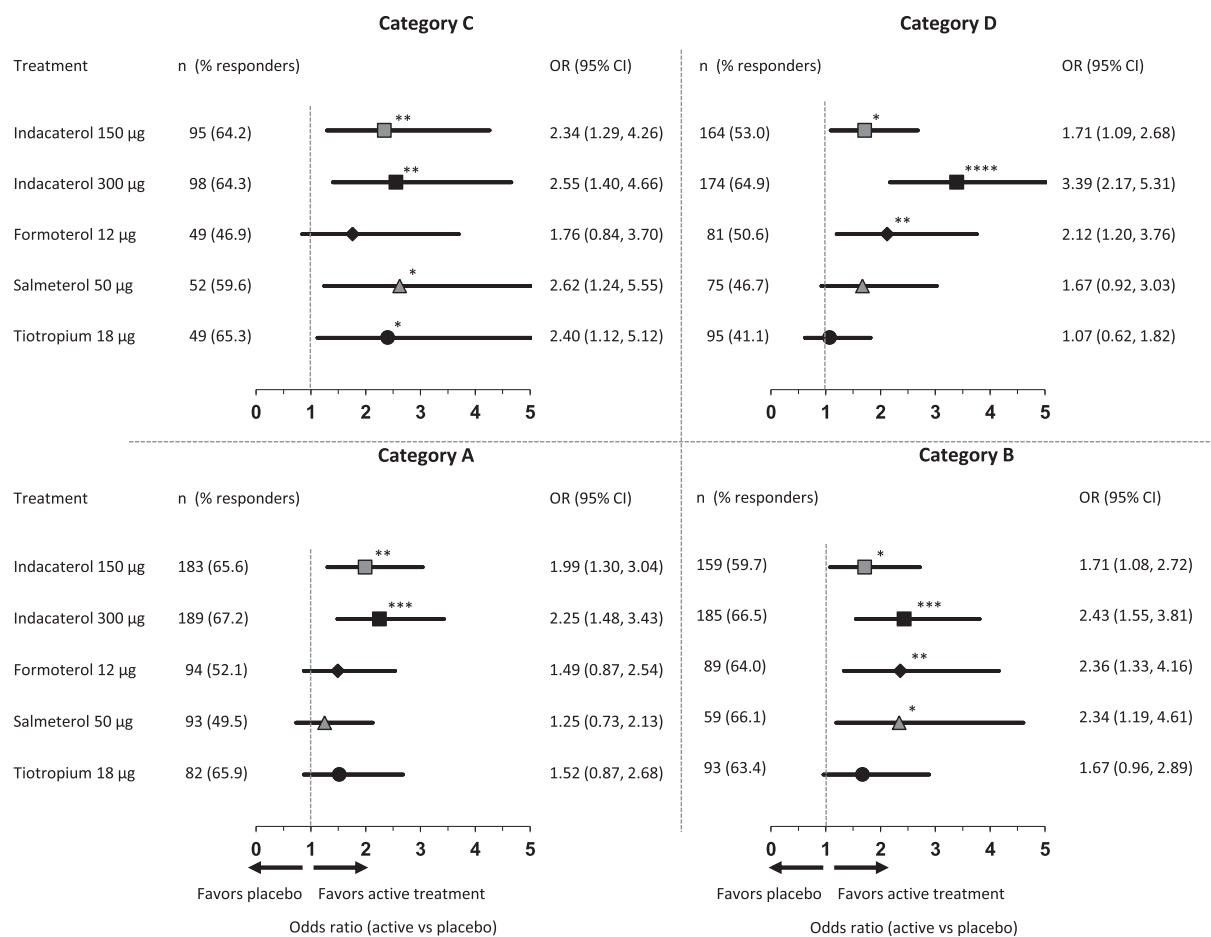


Fig. 6. Odds ratios (active vs placebo) and associated 95% CI for achieving MCID in TDI total score (–1 point) at Week 26 by GOLD 2011 category. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$ versus placebo. MCID, minimum clinically important difference; TDI, transition dyspnea index.

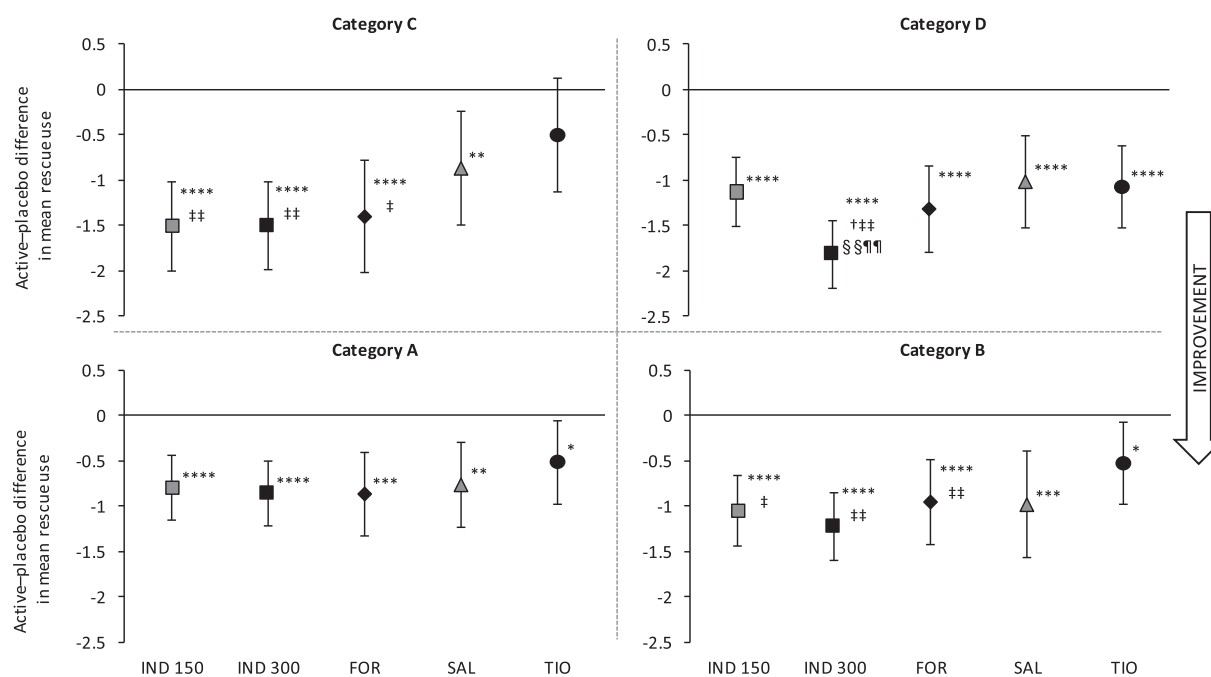


Fig. 7. Mean change from baseline in rescue use (active–placebo differences) by GOLD 2011 category. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$ versus placebo; † $p < 0.05$ for difference versus formoterol; ‡ $p < 0.05$; § $p < 0.01$ for difference versus tiotropium; ¶ $p < 0.01$ for difference versus salmeterol; * $p < 0.01$ versus indacaterol 150 µg. FOR, formoterol 12 µg; IND 150, indacaterol 150 µg; IND 300, indacaterol 300 µg; SAL, salmeterol 50 µg; TIO, tiotropium 18 µg.

Treatment of COPD requires consideration of multiple factors including lung function, patient symptoms, and future risk of exacerbations. For this reason, treatments should be selected according to individual patient requirements in order to provide the greatest benefit. Given the lack of data from clinical trials specifically designed around the current GOLD classification, the current analysis provides perhaps the best available category of data to support the choice of therapies.

There are some limitations of the present study including that it was a post-hoc analysis. Administration of tiotropium as open-label may have an effect on patient-reported outcomes such as dyspnea and health status, although a 12-week study using blinded tiotropium confirmed a statistically significant improvement of indacaterol on TDI and SGRQ compared with tiotropium [15]. Analysis of indacaterol trial data has also shown that in subjective measures, such as SGRQ and TDI, only minimal bias is introduced by the use of open label tiotropium [16]. Further, the GOLD categories could not be exactly modeled according to the GOLD 2011 strategy, as the original studies did not capture the number of exacerbations in the previous year, only whether there were exacerbations or not. In terms of exacerbations, GOLD 2011 defined “high risk” as ≥ 2 exacerbations in the previous year. Of note, according to the updated (2014) document, a patient who experienced a single exacerbation resulting in hospitalization would be considered at high risk of future exacerbations. Finally, the incidence of adverse events was not analyzed in this post-hoc analysis, however in the original studies the incidence of adverse events was shown to be comparable across the treatment groups and similar to placebo [5–7].

5. Conclusions

In conclusion, pooling data from several studies and grouping patients by GOLD category allows comparison of the effectiveness of long-acting bronchodilators across a spectrum of COPD disease severity. In this pooled analysis, indacaterol, a once-daily LABA, was effective in improving lung function, dyspnea, and rescue medication use across all four recently defined GOLD categories.

Acknowledgments

We acknowledge Dr. Adam Tearle, Novartis Healthcare Pvt. Ltd., India, for medical writing support. We also thank all the clinical investigators and study coordinators at the participating centers and all the patients who participated in the studies.

Disclosures

HAMK has, within the last five years, through his input, received honoraria for lectures and consulting, as well as fees per patient for conducting trials from Almirall, Astra Zeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Novartis, Pfizer, Novartis, and Takeda.

GD has, within the last five years, received honoraria for lectures from Astra Zeneca, Novartis, PneumRx, Chiesi, for conducting clinical studies from PneumRx, Holaira, Novartis, GlaxoSmithKline, Boehringer Ingelheim.

RD has given lectures or served on advisory boards for Boehringer-Ingelheim, Astra Zeneca, GlaxoSmithKline, Vectura,

ALK-Abelló, Airsonett, MSD, Novartis, and eElevation and conducted clinical trials for ALK-Abelló, Stallergen, Pfizer, Boehringer-Ingelheim, Astra Zeneca, and Novartis.

JFD is a consultant to Almiral, Astra Zeneca, Boehringer Ingelheim, GSK, Novartis, Sunovion and is on Data and Safety Monitoring boards for NIH, Novartis, Merck, Gilead, Pearl, Teva.

OK has, within the last five years, received honoraria for lectures from Astra Zeneca, Boehringer Ingelheim, Novartis, and Meda Pharma; for consulting from Pfizer and Novartis; for conducting clinical studies from Almirall, Astra Zeneca, Bayer, Boehringer Ingelheim, Cephalon, Chiesi, GlaxoSmithKline, Mundipharma, and Novartis.

DY and DL are employees of Novartis.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.pupt.2015.02.008>.

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